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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,020	10/16/2001	Daniel S. Kohane	0492611-0417 (MIT 8966)	5504

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EXAMINER	
FUBARA, BLESSING M	
ART UNIT	PAPER NUMBER
1618	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/21/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/981,020	KOHANE ET AL.	
	Examiner	Art Unit	
	Blessing M. Fubara	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,7-65,80,81 and 84-97* is/are pending in the application.

4a) Of the above claim(s) *21,22,26,29,31-36 and 38-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 7-20, 23-25, 27, 28, 30, 37, 46-65 and 80, 81, 84-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges receipt of request for extension of time, amendment and remarks filed 10/02/06. Claims 1, 2, 7-65, 80, 81, 84, 85 and new claims 86-97 are pending and of these claims, 21, 22, 26, 29, 31-36 and 38-45 are withdrawn from consideration.

Previous rejections that are not reiterated herein are withdrawn.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 92 and 95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is new matter rejection.

The specification at paragraph [0145] of the published specification supports proportion of DPPC : albumin : lactose : bupivacaine of 54 : 19 : 18 : 10. New claims 92 and 95 recite proportions/ratio for generic lipid, protein, sugar and active agent while the specification as filed is specific to specific lipid, protein, sugar and active agent. Thus, the as filed specification does not provide support for the generic

The rejection may be overcome by removing the new matter from the claims 92 and 95.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 2, 7, 12-20, 23-25, 27, 28, 30, 37, 46-65 and 80, 81, 84, 85 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein et al. (US 6,423,345). New claims 86-92 are included in the rejection. Therefore, claims 1, 2, 7, 12-20, 23-25, 27, 28, 30, 37, 46-65, 80, 81, 84, 85 and 86-97 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein et al. (US 6,423,345).

Bernstein discloses polymer matrices in the form of microparticles, wherein a lipid, or amphiphilic polymer or other hydrophobic compounds are integrated into polymeric matrix (abstract) and the matrix can be formed of synthetic or natural polymers, including proteins, such

as albumin, and polysaccharides (sugars) and vasodilators (column 3, line 31 to column 4, line 22; column 6, line 56 to column 7 line 5).

Bernstein includes therapeutic and prophylactic agents among the active agents, which can be incorporated into the matrix (column 6, line 56 to column 7, line 5). The microparticles of Bernstein can be administered as powder, or formulated in tablets or capsules, or suspended in a solution with pharmaceutically acceptable carriers (column 9, lines 35-47).

The agents described in Bernstein are those that may be labeled with a fluorescent label or an enzymatic or chromatographically detectable agents (column 6, lines 61-63) are diagnostic agents. With respect to the amounts of lipid, protein and sugar claimed in claims 48-56 of the instant application, Bernstein teaches that the content of the lipid in the matrix is 0.01-60% in relation to the content of the polymer (column 6, lines 18-21) and the amount of polymer (protein) is 0.1-60% (column 4, lines 62-64). Therefore, the patent contemplates an amount of lipid up to 36%. With respect to the size of the claimed size of the microparticles claimed in claims 57-60 and 80 of the application, Bernstein discloses that the microparticles of the invention are manufactured with a diameter suitable for the intended route of administration, and discloses particles for intravascular administration having a diameter of 0.5 to 8 microns (column 2, lines 20-27). With regard to the particle size claimed in instant claim 61, Bernstein is deficient in the sense that the patent fails to disclose particles smaller than 0.5 microns. Applicant has not established comparable example in the specification to demonstrate that the claimed small size provides some unusual and/or unexpected results. It appears to the examiner that the smaller size of particles does nothing additional to the compositions of the invention,

especially in view of the teachings of the prior art, that the microparticles of the invention can be administered by any route, including administration to the lungs (column 9, lines 56-63).

With respect to the method of preparing the microparticles claimed in claim 62, Bernstein discloses that the microparticles of the invention can be produced by spray drying the polymer solution formed by dissolving the polymer (protein) and the lipid in the appropriate solvent, dispersing the active agent into the polymer solution (column 8, lines 18-33). With regard to the method of administering an agent claimed in claims 63-65 of the application, Bernstein discloses that the microparticles are combined with a pharmaceutically acceptable carrier and administered to a patient by injection into a blood vessel, subcutaneously, intramuscularly or orally (column 9, line 64 to column 10 line 6). Oral administration implies placing the microparticles in the oral cavity of the patient, thus the patent contemplates placing the microparticles in a body cavity of the patient, as claimed in claim 65 of the instant application. With respect to the ratio of lipid to protein to sugar claimed in claim 47 and also to the ratios in claims 92 and 95 of the application, it is noted that applicants have no demonstration that the ratio of lipid claimed in the instant application provides unusual/unexpected results and there is no comparable example in the specification to demonstrate that the claimed ratio of lipid provides some unusual and/or unexpected results. It appears to the examiner that the higher ratio of lipid does nothing additional to the compositions of the invention, especially in view of the teachings of the prior art, that the hydrophobic compound integrated in the polymeric matrix modifies the diffusion of water into the microparticle and the diffusion of solubilized drug out of the matrix (column 2, lines 8-11).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Bernstein to prepare the microparticles of Bernstein with the expectation for controlled delivery of drugs.

Response to Arguments

6. Applicant's arguments filed 10/02/06 have been fully considered but they are not persuasive.

Applicant disagrees with the rejection and argues that PLGA is shown in applicants specification to produce statistically significant increased inflammatory response at the site of injection as compared with the lipid-protein-sugar particles after two and eight weeks of administration. Bernstein includes extensive laundry list of possible matrix materials and specifically exemplifies PLGA-lipid. Applicant does admit that PLGA could be used as a component in the claimed microparticle, but also points out that the PLGA when it is used is not the primary component while the PLGA is the primary component in Bernstein.

Response:

There is really no extensive laundry of polymer for use in the invention of Bernstein. Synthetic polymers are listed at column 3, line 45 to column 4 line 12 and this list is not extensive. Bernstein further discloses preferred biodegradable polymers to include polymers of hydroxy acids such as lactic acid and glycolic acid, copolymers with PEG, polyanhydrides, poly(ortho)esters, polyurethanes, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprtolactone), blends and copolymers thereof (column 4, lines 13-17). Bernstein also contemplates the use of natural polymers, biodegradable and non-degradable polymers (column

3, lines 32 and 33; column 4, lines 19-30). The one Example in Bernstein is an exemplification of one of the embodiments and the disclosure that other biodegradable and non-biodegradable polymers can be used to formulate matrices. The claimed matrix comprises lipid, protein and sugar. The matrix of Bernstein also contains lipid, protein and sugar as described in the rejection. Therefore, Bernstein is not only directed to the use of PLGA but contemplates the use of other polymer.

7. Claims 8-11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein et al. (US 6,423,345) and further in view of Goldenheim et al. (US 6,534,081).

The teachings of Bernstein et al. have been summarized above. The prior art is deficient in the fact, that it does not specifically include the anesthetics recited in claims 8-10 of the application and anticonvulsant agents, as claimed in claim 11, among the therapeutic agents encapsulated in the microparticles of the invention. Goldenheim provides sustained release dosage forms comprising a local anesthetic and an augmenting agent, and includes bupivacaine, dibucaine, tetracaine and lidocaine among the preferred local anesthetics used in the invention (column 3, line 50 to column 4, line 51). Goldenheim teaches that the local anesthetic is prepared in matrices of controlled release injectable microspheres (column 5, lines 60-64), and the formulations of the invention are suitable for administration in all body spaces and cavities (column 6, lines 55-59). Goldenheim discloses formulations comprising microparticles comprising a local anesthetic, an augmenting agent and a sustained release polymer selected from synthetic polymers, proteins, polysaccharides and combinations thereof (column 7, lines 20-47). Thus, the patent provides the general teachings that local anesthetics can be delivered by microparticle compositions and specifically discloses the compounds recited in claims 8-10 of

the instant application. With respect to claim 11, Goldenheim includes anticonvulsants among the augmenting agents incorporated in the compositions of the invention (column 12, lines 9-12).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Bernstein and the teachings of Goldenheim with the expectation of producing microparticles for the controlled delivery of local anesthetics and anticonvulsant drugs.

Response to Arguments

8. Applicant's arguments filed 10/02/06 have been fully considered but they are not persuasive.

Applicant argues that because Bernstein uses PLGA-lipid in the examples, and applicant's showing in the specification that PLGA injection produces increased inflammation at the site of injection as applicant argued in the preceding section, the Bernstein art falls and combination of Bernstein with Goldenheim would not render claims 8-11 obvious.

Response:

As discussed above, Bernstein contemplates the use of several other polymers and the example is an exemplification of one embodiment. Thus combination of Bernstein and Goldenheim renders claims 8-11 obvious as described above.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER